Office Action Summary	Application No.	Applicant(s)	
	10/528,673	HOSHINO ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-8,13 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-8,13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

In response to the Office Action mailed on 08/11/2006, applicants' filed a response and amendment received on 02/15/2007. Said amendment, amended claims 1, 2, 8 and 16 and cancelled claim 5. Claims 3, 4, 9-12, 14-15 and 17-18 are withdrawn as they are drawn to non-elected inventions. Thus, claims 1, 2, 6-8, 13 and 16 are pending in the instant Office Action and are now under consideration.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Claim Objections

Claims 1, 2 and 8 are objected to, due to the following informality: Claims 1, 2 and 8 recites the phrase "catalytical activity", examiner suggests amending the phrase to recite "catalytic activity". Appropriate correction is required.

Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 6-7 dependent therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "...having the activity to produce L-ascorbic acid", it is not clear to the examiner what are the substrates for a polypeptide sequence comprising an amino acid sequence having 90% sequence identity to SEQ ID NO: 2?. Clarification is required.

Claim Rejections: 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 6-8, 13 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of L-ascorbic acid comprising: contacting an enzyme having the amino acid sequence of SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1, said polypeptide expressed in a specific strain of *E.coli* JM 109 having the activity to produce L-ascorbic acid from substrates L-gulono-1,4-lactone/L-gulonic acid from L-gulose and from L-galactono-1,4-lactone/L-galctonic acid or conversion of substrate L-galctose to L-galactono-1,4-lactone/L-galactonic acid and L-ascorbic acid under suitable culture conditions (as in Examples: 1-4, pages 8-10; and culture conditions: lines 15-28, page 6 of specification). However, the specification does not reasonably provide enablement for a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 to from any source including variants, mutants and recombinants and encoded by the polynucleotide of SEQ ID NO: 1 or an amino acid encoded by a polynucleotide that hybridizes to SEQ ID NO: 1 under stringent hybridization conditions and said polypeptide under any conditions i. e., said polypeptide expressed in any cellular context is able to produce L-ascorbic acid in a process for the production of L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which said substrates are allowed to react with said enzyme. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-2, 6-8, 13 and 16 are so broad as to encompass a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 to from any source including variants, mutants and recombinants and encoded by the polynucleotide of SEQ ID NO: 1 or an amino acid encoded by a polynucleotide that hybridizes to SEQ ID NO: 1 under stringent hybridization conditions and said polypeptide under any conditions i. e., said polypeptide expressed in any cellular context is able to produce L-ascorbic acid in a process for the production of L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which said substrates are allowed to react with said enzyme. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines

its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to the production of L-ascorbic acid comprising: contacting an enzyme having the amino acid sequence of SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1, said polypeptide expressed in a specific strain of *E.coli* JM 109 having the activity to produce L-ascorbic acid from substrates L-gulono-1,4-lactone/L-gulonic acid from L-gulose and from L-galactono-1,4-lactone/L-galctonic acid or conversion of substrate L-galactose to L-galactono-1,4-lactone/L-galactonic acid and L-ascorbic acid under suitable culture conditions (as in Examples: 1-4, pages 8-10; and culture conditions: lines 15-28, page 6 of specification). The specification is limited to teaching the use of an enzyme having the amino acid sequence of SEQ ID NO: 2 with the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme, but provides no guidance with regard to the making of other variants, mutants and recombinants from any source or with regard to other uses in a process for production L-ascorbic acid wherein said polypeptide is expressed in any cellular context and said cells are able to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which any substrate i. e., selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-

1,4-lactone and L-talonic acid are allowed to react with said enzyme. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 to from any source including variants, mutants and

recombinants and encoded by the polynucleotide of SEQ ID NO: 1 or an amino acid encoded by a polynucleotide that hybridizes to SEQ ID NO: 1 under stringent hybridization conditions and said polypeptide under any conditions i. e., said polypeptide expressed in any cellular context is able to produce L-ascorbic acid in a process for the production of L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which said substrates are allowed to react with said enzyme, because the specification does not establish: (A) regions of SEQ ID NO: 2 protein/polynucleotide structure that can be modified without affecting the activity to produce L-ascorbic acid in any cellular context and under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme; (B) the general tolerance of the polypeptide with SEQ ID NO: 2 and the encoding polynucleotide to modification and extent of such tolerance; (C) a rational and predictable scheme for modification with any amino acid residue or the respective codon in the encoding polynucleotide with an expectation of obtaining the desired biological function i.e., the activity to produce L-ascorbic acid under any cellular context and specific defined process conditions such as pH, temperature and time in which any substrate i. e., selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid are allowed to react with said enzyme; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides with an enormous number of modifications for a

process of producing L-ascorbic acid. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Furthermore, a skilled artisan would not expect all the substrates listed in the claims to yield L-ascorbic acid by contacting with a polypeptide having 90% identity with SEQ ID NO: 2, as the claimed substrates may require the conversion to intermediates (this process may require other enzymes), that can be acted upon by a polypeptide of SEQ ID NO: 2 and to determine whether any polypeptide having 90% sequence identity to SEQ ID NO: 2 would be active in converting the said intermediates in addition to other enzymes required for conversion of substrates would be unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' have traversed this rejection and the claimed invention is enabled if any person skilled in the art can make and use the invention without undue experimentation and need only routine experimentation as the burden lies with the examiner to provide reasons for the uncertainty of the enablement. Applicants' arguments have been considered and the following body of scientific publication supports the basis for rejection.

While methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan, producing variants capable of being used in a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-

idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 from any source including variants, mutants and recombinants and encoded by the polynucleotide of SEQ ID NO: 1 or an amino acid encoded by a polynucleotide that hybridizes to SEQ ID NO: 1 under stringent hybridization conditions and said polypeptide under any conditions i. e., said polypeptide expressed in any cellular context is able to produce L-ascorbic acid in a process for the production of L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which any substrate i. e., selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid are allowed to react with said enzyme, requires that one of ordinary skill in the art know or be provided with guidance for the selection of which, of the infinite number of variants, have the activity. Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims, this would clearly constitute **undue** experimentation. Guo et al., (PNAS, 2004, Vol. 101 (25): 9205-9210) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (p 9206, paragraph 4). Guo et al., (*supra*) further show that the percentage of active mutants for multiple mutations appears to be exponentially related to this by the simple formula $(.66)^{X}$ X 100% where **x** is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 90% identity allows up to 58 mutations within the 579 amino acids of SEQ ID NO: 2 and, thus, only $(0.66)^{58}$ X 100% or

3.44×10^{-9} % of random mutants having 90% identity would be active. Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a reasonable number of active mutants within hundred thousand inactive mutants (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish). But finding a few mutants within several billions or more, as in the claims to 90% identity, would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Applying this estimate to the instant protein, a functional equivalent thereof with 90% sequence identity, as recited in Claims 1-2, 6-8, 13 and 16, an extremely low number of active mutants will be present among an enormously large number of inactive mutants and as such screening for these active mutants would be burdensome and undue experimentation when there is no guidance provided in the specification.

Maintained-Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 6-8, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Asakura et al., (EPO 832974 A2, date of publication 01/04/1998) when given the broadest interpretation. Claims 8 and 16 are directed to a process for the production of L-ascorbic acid

comprising: contacting an enzyme with a substrate selected from the group consisting of, L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence 90% identical to SEQ ID NO: 2 encode by a polynucleotide of SEQ ID NO: 1, with the activity to produce L-ascorbic acid (claims 1-2) and to a process for producing L-ascorbic acid comprising contacting a substrate which is selected from L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid with an enzyme derivable from of *G.oxydans* DSM 4025 and isolating L-ascorbic acid from the reaction, wherein said enzyme has the following physico-chemical properties: a) molecular weight of about 60, 000 Da on SDS-PAGE; b) substrate specificity for primary and secondary alcohols and aldehydes; c) pH stability at a pH of about 6 to about 9; d) pH optimum of about 8.0; and e) inhibited by Cu^{2+}, Zn^{2+}, Mn^{2+}, $Fe^{2+}$and Fe^{3+} under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme (claims 5-8, 13 and 16).

Asakura et al., *(supra)* disclose the purification, kinetic profiles and physico-chemical characterization of a polypeptide designated as Enzyme B from *G.oxydans* DSM 4025 that has 100% sequence homology to SEQ ID NO: 2 of the instant application with identical physico-chemical properties and substrate specificity for primary and secondary alcohols, optimal pH range, pH stability, thermal stability and effect of metals and inhibitors on the activity of said enzyme (Table: 1, 2, 3, 4 and 5, page 10, lines 29-30 gives the pH range for the reaction to be about 6.0 to about 9.0 and the temperature range for the reaction of about 10^0C to about 50^0C,

preferably of 20^0C to 40^0C). Furthermore, Table 10, page 23 discloses L-idose as a substrate for Enzyme B and the formation of L-idonic acid and the use of said enzyme in a process for the production of L-ascorbic acid and the intermediates of L-ascorbic acid (Abstract section). Therefore the reference of Asakura et al., anticipates the claims 1-2, 6-8, 13 and 16 as written.

Applicants' have traversed the rejection with the argument that " The specific use of the recited enzyme for a direct one step-conversion of claimed substrates into L-ascorbic acid is not disclosed by Asakura". Applicants' arguments have been considered and found to be non-persuasive for the following reasons. The claims as written "A process for production of L-ascorbic acid comprising: is interpreted as "open language" and therefore the process for production of L-ascorbic acid can comprise other elements in the reaction and hence reads on the disclosure of Asakura et al.,. Furthermore, neither the claims as written nor the specification explicitly states that the said process for the production of L-ascorbic acid is a direct one step-conversion of claimed substrates into L-ascorbic acid (see also 112, First paragraph enablement rejection). The said process of L-ascorbic acid was carried out under specific cellular context, i.e., production of L-ascorbic acid in a process comprising: contacting an enzyme having the amino acid sequence of SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1, said polypeptide expressed in a specific strain of *E.coli* JM 109 having the activity to produce L-ascorbic acid from substrates L-gulono-1,4-lactone/L-gulonic acid from L-gulose and from L-galactono-1,4-lactone/L-galctonic acid or conversion of substrate L-galactose to L-galactono-1,4-lactone/L-galactonic acid and L-ascorbic acid under suitable culture conditions (as in Examples: 1-3, pages 8-10; and culture conditions: lines 15-28, page 6 of specification) and therefore said bacteria may provide other necessary enzymes either for the production of

intermediate products of L-ascorbic with claimed substrates or for the final conversion of the intermediate products to L-ascorbic acid.

New-Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 8, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Sugisawa et al., (1995) when given the broadest interpretation. Claims 2, 8, 13 and 16 are directed to a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of, L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, with an enzyme derivable from of *G.oxydans* DSM 4025 and converting the said substrates into L-ascorbic acid by catalytical activity of the enzyme under suitable culture conditions and isolating L-ascorbic acid from the reaction, wherein said enzyme has the following physico-chemical properties: a) molecular weight of about 60, 000 Da on SDS-PAGE; b) substrate specificity for primary and secondary alcohols and aldehydes; c) pH stability at a pH of about 6 to about 9; d) pH optimum of about 8.0; and e) inhibited by Cu^{2+}, Zn^{2+}, Mn^{2+}, $Fe^{2+}$and Fe^{3+} under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme.

Sugisawa et al., (*supra)* disclose the purification, kinetic profiles and physico-chemical characterization of a polypeptide derived from *G.oxydans* DSM 4025 that produced L-ascorbic

acid from L-gulono-γ-lactone said enzyme consisted of 3 subunits of molecular weight of about 61,000 +/- 1000, 32,500 +/- 1000 and 16,500 +/- 500 with identical physico-chemical properties and substrate specificity, optimal pH range, pH stability, thermal stability and effect of metals and inhibitors on the activity of said enzyme (Abstract section). Furthermore, Tables: I, II, IV, V, VI and VII disclose production of L-ascorbic acid, substrate specificity, effects of temperature, pH and various metals on the activity of said enzyme. Claims 2, 13 and 16 are included in the rejection although said claims recite specific SEQ ID NO: 2 and the activity of said polypeptides under specific pH and temperature, because examiner interprets these properties to be inherent in the isolated polypeptide. Therefore the reference of Sugisawa et al., anticipates the claims 2, 8, 13 and 16 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Maintained- Claim Rejections 35 USC § 103

Previous rejection of claims 1, 2, 6-8, 13 and 16 rejected under 35 U.S.C. 103(a) as being unpatentable over Asakura et al., (EPO 832974 A2, date of publication 01/04/1998) and further in view of Bourdant et al., (Enzyme Micro. Technol., 1990, Vol. 12, pages 322-329) and Hancock et al., (TRENDS in Biotechnol., 2002, Vol. 20 No. 7, pages 299-305) is maintained.

The applicants' have traversed the rejection with the arguments that the instant invention is a single step microbial process, a single enzyme is able to produce L-ascorbic acid from the substrates claimed in the instant invention and the cited prior art requires a combination of enzymes to produce the L-ascorbic acid. Applicants' arguments have been considered but are found to be non-persuasive for the following reasons: 1) the claims as written "comprising" is interpreted as "open language" and therefore the process may involve additional enzymes or processes to produce the final product L-ascorbic acid and nowhere in any of the claims is it explicitly stated that the claimed process is a one-step process for the production of L-ascorbic acid; 2) only support in the specification for production of L-ascorbic acid is a process comprising: contacting an enzyme having the amino acid sequence of SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1, said polypeptide expressed in a specific strain of *E.coli* JM 109 having the activity to produce L-ascorbic acid from substrates L-gulono-1,4-lactone/L-gulonic acid from L-gulose and from L-galactono-1,4-lactone/L-galctonic acid or conversion of substrate L-galactose to L-galactono-1,4-lactone/L-galactonic acid and L-ascorbic acid under suitable culture conditions (as in Examples: 1-4, pages 8-10; and culture conditions: lines 15-28, page 6 of specification) and said bacterial strain is interpreted to comprise many other enzymes that are involved in the conversion of other claimed substrates into intermediates, said intermediates are acted upon by enzyme having the amino acid sequence of SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1 to form L-ascorbic acid.

Conclusion

None of the claims are allowable.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claims 1, 2 and 8 are objected to, due to informalities.

2) Claim 1 and claims 6-7 dependent therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3) Claims 1-2, 6-8, 13 and 16 are rejected under 35 U.S.C. 112, first paragraph for enablement.

4) Claims 1-2, 6-8, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Asakura et al., (EPO 832974 A2, date of publication 01/04/1998) when given the broadest interpretation.

5) Claims 2, 8, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Sugisawa et al., (1995) when given the broadest interpretation.

6) Claims 1, 2, 6-8, 13 and 16 rejected under 35 U.S.C. 103(a) as being unpatentable over Asakura et al., (EPO 832974 A2, date of publication 01/04/1998) and further in view of Bourdant et al., (Enzyme Micro. Technol., 1990, Vol. 12, pages 322-329) and Hancock et al., (TRENDS in Biotechnol., 2002, Vol. 20 No. 7, pages 299-305).

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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